UNIVERSITY OF WISCONSIN-MADISON
COLLEGE OF AGRICULTURAL AND LIFE SCIENCES

Impact of New Genomic Technologies on Herd Improvement and the Dynamics of Replacement Programs

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Outline

- How does genomics work?
- How accurate are the genomic predictions?
- Is there a way to reduce genotyping costs?
- Are some applications cost-effective today?
- What new applications will be developed?

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Bovine Genome Sequence

AGTCCATGGGGTTATAGAGTCAGACACAGTGGAGTCACACACATACACACG
TCACCACGCCGAATTAAGGCGGGGCTGAGACAAGGGCAGGTGAGGCCTCC

genotype
haplotype

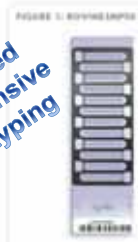
- 30 pairs of chromosomes
- 3 billion base pairs (potential SNPs)

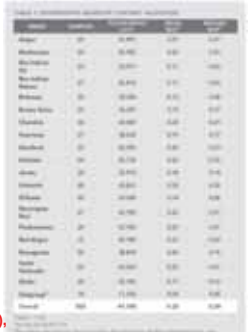
Single Nucleotide Polymorphism

Courtesy of George Wiggans, USDA-AIPL

"SNP Chips"

Automated + Inexpensive Genotyping

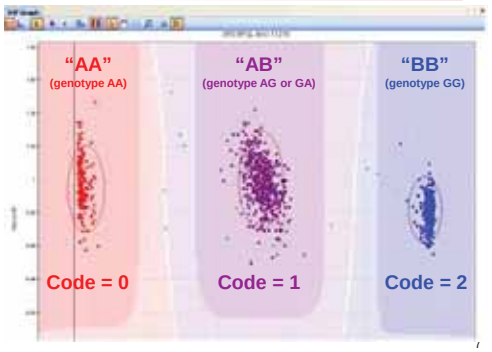




Also Illumina 3K, LD (6.9K), HD (778K), and Affymetrix HD (620K) SNP chips

Example SNP

(located at 2,153,905 base pairs on chromosome 13)



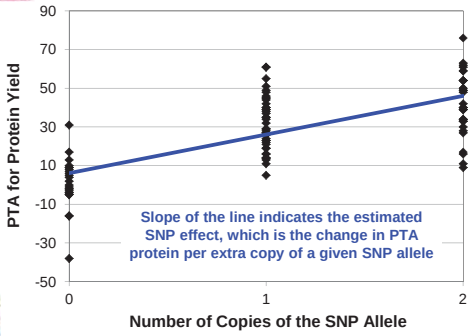
SNP Genotype of Elevation

(part of chromosome 1)

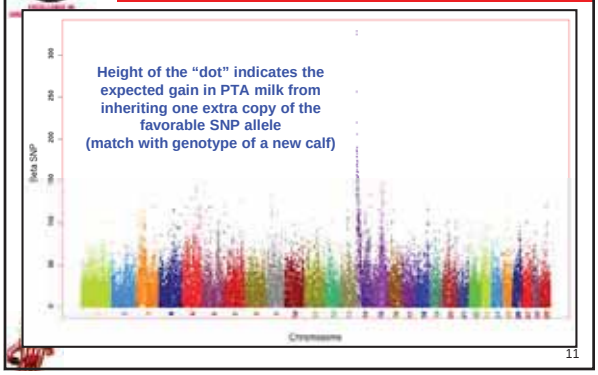
10001112200200121110111121111011100112110002012200222011112021012001211221100211120011100101101102200110022011012002020121112221020100111000112202212221120211201202010020202000 11000021220020022101200002220 20102100022000220100002011000 12112122200200020020201222 20011011101120020220200011120 11001111102111102111220001 11011202102102121101102212200 02110001110021021100222 21221121112002011020200122220 00220002001002000111011001211021212111201010121022010101111102110211211101101200111102111011111220121012121101022202021211222120222002121210121210201100111222121101

Reference Population

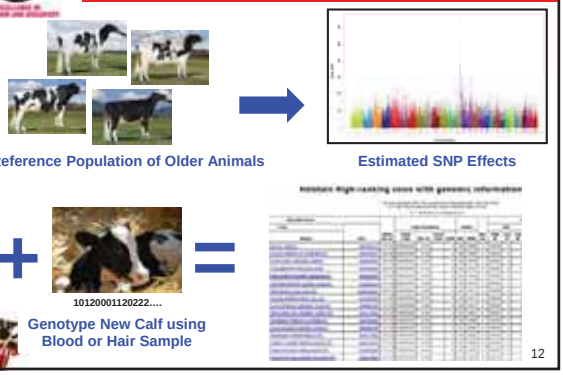
Estimating SNP Effects



Manhattan Graph of SNP Effects



Genomic PTA (GPTA) for a Young Calf



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Cooperative Dairy DNA Repository

Lots of DNA Samples

19,000 bulls with DNA samples in the CDDR

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National Genetic Evaluation Program

Lots of Phenotypes

6 million daughter performance records at USDA-AIPL

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USDA-AIPL Validation Study

	HOL	JER	BSW
Training Data (2004) ⟵ for estimating SNP effects			
Bulls with progeny	4,422	1,149	472
Cows with records	947	212	40
Total	5,369	1,361	512
Testing Data (2009) ⟵ for checking the accuracy of predictions			
Bulls with no progeny	2,035	388	150

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Gains in Reliability, by Trait

(gain above parent average reliability ~35%)

	HOL	JER	BSW
Lifetime Net Merit	24%	8%	9%
Milk Yield	26%	6%	17%
Fat Yield	32%	11%	10%
Protein Yield	24%	2%	14%
Fat %	50%	36%	8%
Protein %	38%	29%	10%
Productive Life	32%	7%	12%
Somatic Cell Score	23%	3%	17%
Daughter Pregnancy Rate	28%	7%	18%
Final Score	20%	2%	5%
Udder Depth	37%	20%	8%

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Picking the Right Calf with Genomics

Full Brothers	Family Size	Holstein	Jersey
Best Genomic PTA in November 2004 = Best Progeny Test PTA in January 2009	2	86/126 (68%)	24/34 (71%)
	3	5/10 (50%)	5/8 (63%)
Maternal Half Brothers	**Family Size**	**Holstein**	**Jersey**
Best Genomic PTA in November 2004 = Best Progeny Test PTA in January 2009	2	138/210 (66%)	28/41 (68%)
	3	43/66 (65%)	10/16 (63%)
	4	12/26 (46%)	3/8 (38%)
	5	5/12 (42%)	2/3 (67%)

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AI Bulls and Elite Cows

- Genomic proofs became official in January 2009
- Genomic evaluations for young bulls now have reliability similar to early first-crop evaluations
- AI organizations are marketing hundreds of genome-tested 2, 3, or 4 year-old bulls: You should use these bulls, but use fewer units per individual bull to mitigate risk
- Genotypes are often required for bull dams or other animals that are being marketed

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What about Commercial Females?

- At current prices, the 50K and HD chips are limited to applications involving males and elite females
- A chip with 300 to 3000 selected or equally spaced SNPs might deliver a substantial portion of the gain for a fraction of the price
- Applications may include: parentage discovery, selection among replacement heifers, preliminary screening of potentially elite young bulls and heifers, and genomic mating programs

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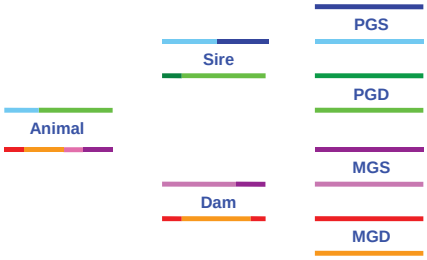
Recombination



SNPs pass from one generation to the next in chunks (haplotypes), not independently

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What is Genotype Imputation?

Aoccdrnig to rscheearch at Cmabrigde Uinervtisy, it deosn't mttaer in waht oredr the ltteers in a wrod are, the olny iprmoetnt tihng is taht the frist and lsat ltteer be at the rghit pclae. The rset can be a toatl mses and you can sitll raed it wouthit a porbelm. Tihs is bcuseae the huamn mnid deos not raed ervey lteter by istlef, but the wrod as a wlohe.

- Your brain can do this after you learn a language
- Imputation algorithms can do this after they learn which haplotypes are present in the reference population

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Accuracy of Imputed Genotypes

- Use 50K genotypes of 2,542 Jersey bulls, cows, heifers, and calves born in 1953-2006 as the reference panel for building haplotypes
  → "Training Set"
- Mask and impute genotypes for 20, 40, 80, 90, 95, 98, or 99% of SNPs in 604 Jersey bulls, cows, heifers, and calves born in 2007-2009 to evaluate the accuracy of genotype imputation
  → "Testing Set"

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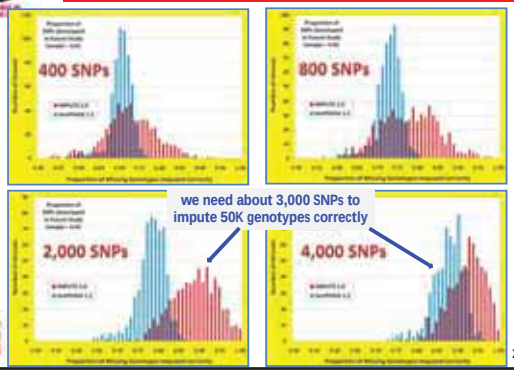
Accuracy of Imputed Genotypes



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Accuracy of Imputed PTAs

- Use 50K genotypes and 2006 phenotypes for 1,446 Jersey bulls with progeny in May 2006 as reference animals to build haplotypes and estimate SNP effects
  → "Training Set"
- Mask and impute 93, 96, 98, or 99% of SNPs in 316 Jersey bulls with progeny in April 2009, compute genomic PTAs from imputed SNPs and evaluate accuracy of the predictions
  → "Testing Set"

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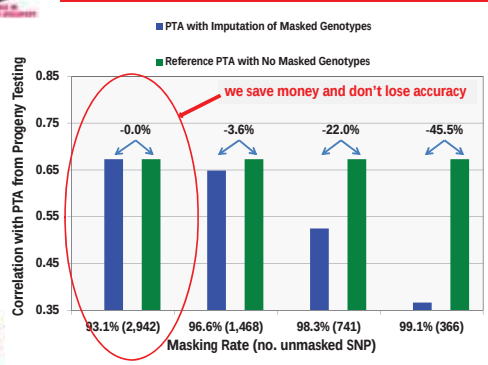
Accuracy of Imputed PTAs: Milk



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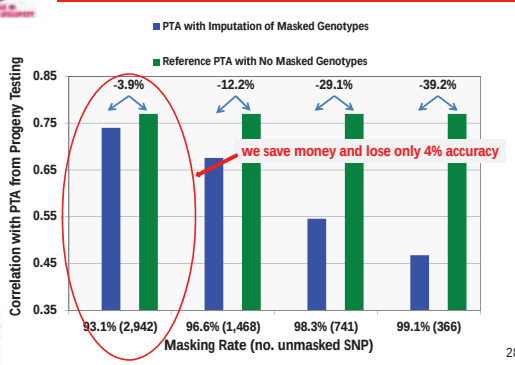
Accuracy of Imputed PTAs: Protein %



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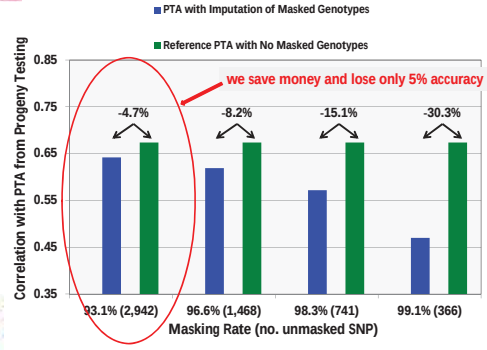
Accuracy of Imputed PTAs: Fertility



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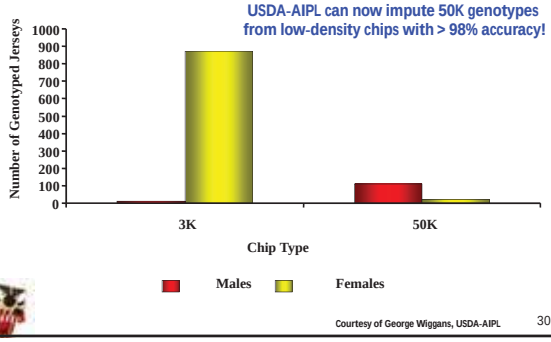
Jersey Cattle Genotyped in May 2011



Courtesy of George Wiggans, USDA-AIPL

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Strategies for Genotyping Females

- Test the whole herd

- Screen potentially elite animals for marketing

- Screen potentially inferior animals for culling

- Screen animals "at risk" for selection or culling

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Which is the Best Heifer?

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Which is the Best Heifer?

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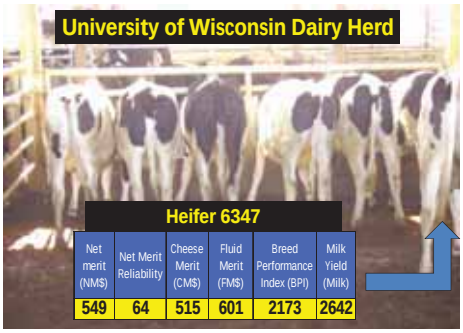
Which is the Best Heifer?



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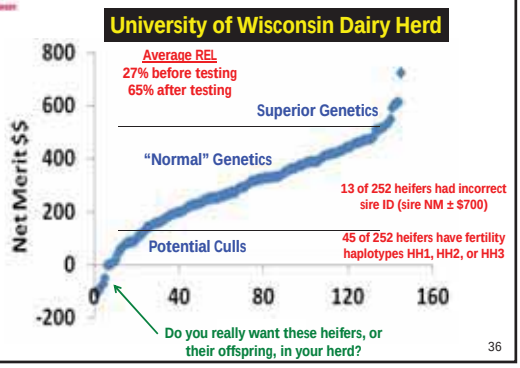
Selection of Replacement Heifers



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Design of Simulation Study

- 1000-cow herd plus replacement heifers
- Replicated 100 times
- Selection for lifetime net merit (NM$)
  - mean = $45, standard deviation = $198
- Genetic trend in PTA = +$28 per year
- Error rate in sire identification = 15%
- Cost of 3K genomic test = $40 per animal

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Reliability without / with Genomics

Age Group	3K + No Pedigree	3K + Sire Known	3K + Full Pedigree
Calves < 12 mo of age	0.00 / 0.48	0.22 / 0.58	0.35 / 0.62
Yearlings 12-24 mo of age	0.00 / 0.49	0.23 / 0.59	0.36 / 0.63
Milking cows 2 yr of age	0.20 / 0.55	0.34 / 0.61	0.42 / 0.64
Milking cows 3 yr of age	0.22 / 0.58	0.38 / 0.63	0.47 / 0.66
Milking cows 4 yr of age	0.24 / 0.60	0.42 / 0.64	0.52 / 0.68
Milking cows 5 yr of age	0.25 / 0.61	0.45 / 0.65	0.55 / 0.69
Milking cows 6 yr of age	0.26 / 0.62	0.47 / 0.66	0.57 / 0.70
Milking cows 7 yr of age	0.27 / 0.63	0.48 / 0.66	0.58 / 0.70

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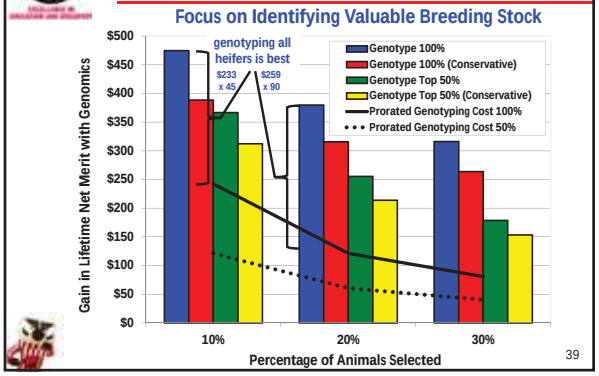
Heifer Calves without Pedigrees (N=450)



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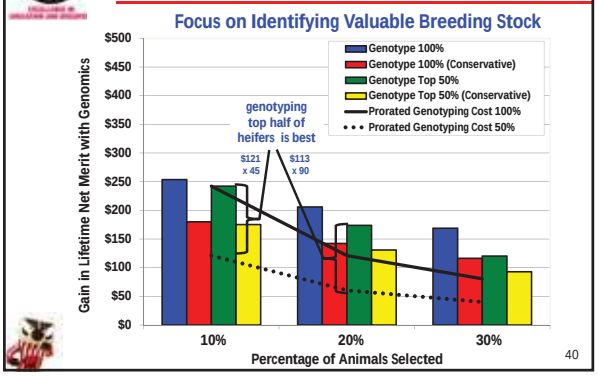
Heifer Calves with Known Sires (N=450)



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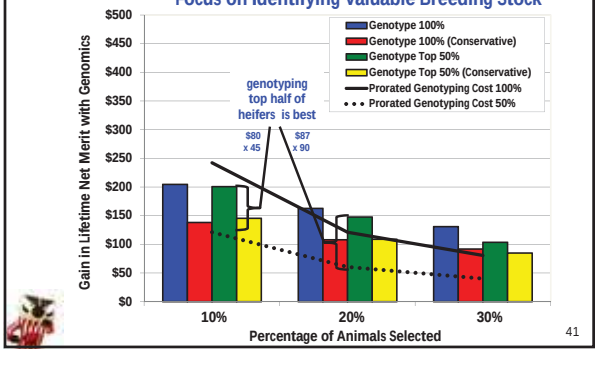
Heifer Calves with Full Pedigrees (N=450)



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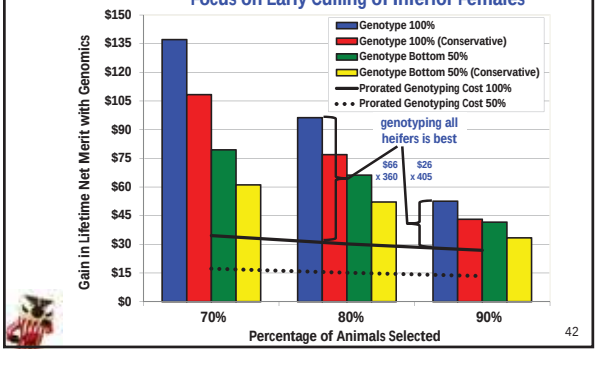
Heifer Calves with no Pedigrees (N=450)



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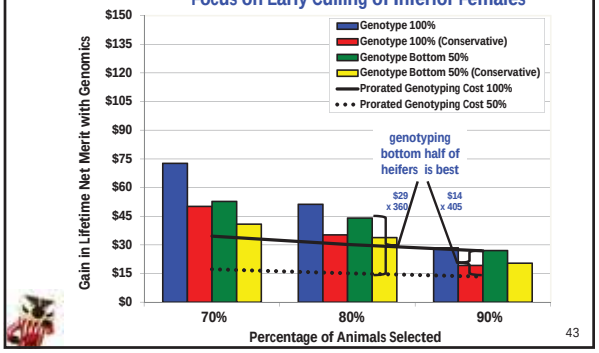
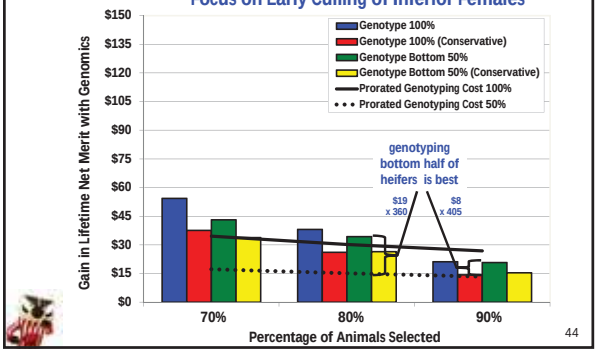
Heifer Calves with Known Sires (N=450)



Heifer Calves with Full Pedigrees (N=450)



What's the Best Strategy?

- Genotyping is most informative for animals with missing or incorrect pedigrees and animals that don't yet have performance data
- Whole-herd genotyping may be cost effective if pedigree and performance data are unavailable
- Pre-sorting animals by pedigree values and testing the subset that are "at risk" for selection or culling may be preferred if accurate pedigrees are available

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- Can we use genomics on commercial farms?
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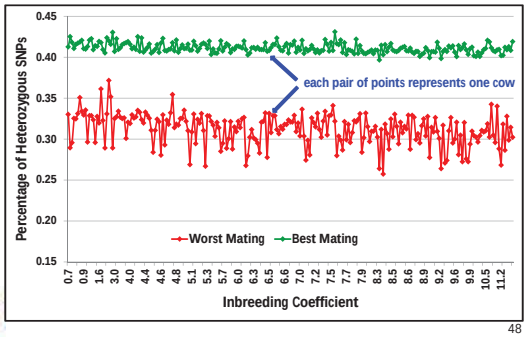
Managing Inbreeding

10 most inbred Jerseys by pedigree

Registration Number	Pedigree-Based Inbreeding Estimate	% Heterozygous SNPs on Gene Chip
JEUSA000115954478	18.6%	28.3%
JEUSA000115486672	17.4%	29.8%
JEUSA000067046058	14.1%	34.4%
JEUSA000114624440	14.0%	34.1%
JEUSA000115011391	14.0%	39.3%
JEUSA000067181563	13.0%	36.5%
JEUSA000115752423	12.6%	36.2%
JEUSA000114669078	12.5%	39.4%
JEUSA000067072713	12.2%	34.5%
JEUSA000115458806	12.2%	34.1%

Mating Programs



Selecting for New Traits

- Measurement of traits like feed intake, hormone levels, immune function, etc. is not possible on tens of thousands of progeny test daughters each year
- These traits can be measured in a reference population of 5,000 to 20,000 cows on experimental farms or collaborating commercial farms
- The resulting SNP effect estimates can be matched with genotypes of young bulls and heifers on other farms for use in selection and management decisions

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Summary: Example Herd Protocol

1. Submit hair or blood cards when heifer is 9-10 months of age
2. If GPTA for Lifetime Net Merit > $600, flush once and then breed to the best available AI bull based on recommended pedigree mating
3. If GPTA for Lifetime Net Merit is $400-600, breed to the best available AI bull using sexed semen
4. If GPTA for Lifetime Net Merit is $200-400, breed to the best available AI bull using conventional semen
5. If GPTA for Lifetime Net Merit is $75-200, use as recipient for a fresh embryo or frozen embryo (if fresh is unavailable), or breed to an AI bull in the 80th percentile (if fresh and frozen are unavailable)
6. If GPTA for Lifetime Net Merit is < $75, breed to an AI bull in the 80th percentile and sell as a short-bred heifer

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